107. A composition according to any one of claims 88 to 95 wherein said HCV genome is capable of selectively hybridizing a HCV polynucleotide or its complement under the following conditions: hybridization in 5 x SSC, 0.1% SDS at 55°C.

108. A composition according to any one of claims 88 to 95 wherein said HCV genome is capable of selectively hybridizing a HCV polynucleotide or its complement under the following conditions: hybridization in 0-50% formamide at 40-42°C.

109. A composition according to any one of claims 88 to 95 further comprising a carrier.

110. A composition according to any one of claims 88 to 95 wherein said immunogenic polypeptide further comprises a carrier.

111. A method of producing an immune response to HCV comprising administering to an animal a composition according to any one of claims 88-95.

112. A method of producing an immune response to HCV comprising administering to an animal a composition according to claim 96.

113. A method of producing an immune response to HCV comprising administering to an animal a composition according to claim 97.

114. A method of producing an immune response to HCV comprising administering to an animal a composition according to claim 98.

REMARKS

Claims 40 to 87 have been canceled. Claims 88 to 114 are pending. With respect to claims 40 to 87, Applicants do not concede that these claims are not patentable and reserve the right to pursue the same or similar subject matter in a continuing application or other related application. Applicants submit that the amendments to the claims are made solely to clarify that which applicants regard as their invention and not to overcome the cited prior art. Cancellation of claims 40 to 87 does not constitute an admission that these claims were not enabled.

Applicants expressly reserve their right under 35 U.S.C. § 121 to file divisional applications directed to the non-elected subject matter during the pendency of this application.

Regarding Amendments to the Claims:

The amendments to the claims are to clarify the nature of the subject matter claimed. Support for the claims is found throughout the specification, therefore, the amended claims do not constitute new subject matter. Specifically, support can be found for the claims, for example, in the following pages and lines of the present specification: page 35, line 1, immunogenic polypeptide; page 147, line 4 to page 151, line 9, substantially isolated form; page 147, line 23 to page 148, line 4, C domain, E domain, NS1, NS2. Also see generally, Section II.C. Preparation of Antigenic Polypeptides and Conjugation with Carrier - page 47, line 24 through page 53, line 36; Section II.D. Preparation of Hybrid Particle Immunogens Containing HCV Epitopes - page 54, line 1 through page 55, line 3; Section II.E. Preparation of Vaccines - page 55, line 5 through page 58, line 29; Section II.F. Dosage and Administration of Vaccines - page 58, line 31 through page 59, line 21; Section II.G. Preparation of Antibodies Against HCV Epitopes - page 59, line 23 through page 61, line 2.

35 U.S.C. § 112, First Paragraph Rejections:

Claims 40-87 have been rejected and the specification has been objected to under 35 U.S.C. § 112, first paragraph as allegedly failing to teach how to make and use the immunogenic polypeptides of the invention. While claims 40-87 have been cancelled, the subject matter of claims 40-87 have been addressed in new claims 88, 93, 94 and 95, and claims dependent thereon. Specifically, claim 88 recites, "an immunogenic composition comprising an immunogenic hepatitis C virus (HCV) polypeptide in substantially isolated form wherein said immunogenic polypeptide comprises a region selected from the group consisting of an envelope domain of an HCV genome. . . ." Claim 93 recites, "wherein said polypeptide comprises a region selected from the group consisting of a core domain of an HCV genome. . . ." Claim 94 recites, "wherein said polypeptide comprises a region selected from the group consisting of a

NS1 domain of an HCV genome. . . ." Claim 95 recites, "wherein said polypeptide comprises a region selected from the group consisting of a NS2 domain of an HCV genome. . . ."

The Office's rejection is based upon the contention that the specification allegedly does not teach how to locate epitopes or immunogenic regions in HCV amino acid sequences or sequences which create a response which is immunospecific to HCV. Applicants respectfully traverse these rejections as well as the supporting remarks.

35 U.S.C. § 112, first paragraph requires a patent to contain a description that enables one skilled in the art to make and use the claimed invention. Atlas Powder Co. v. E. I. du Pont de Nemours & Co., 750 F.2d 1569, 1576 (Fed. Cir. 1984). In the present case, the claims are directed to an immunogenic composition comprising an immunogenic hepatitis C virus (HCV) polypeptide in substantially isolated form wherein said immunogenic polypeptide comprises a region selected from the group consisting of an envelope domain, a core domain, a NS1 domain and a NS2 domain of an HCV genome and immunogenic fragments and combinations thereof.

It is well settled that the initial burden is on the Office to demonstrate that there is a reasonable basis to question the presumptively sufficient disclosure made by an applicant. (see, e.g., In re Wright, 27 USPQ2d 1510 (Fed. Cir. 1993), M.P.E.P. § 2164.04). In other words, the specification must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein. In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971). Furthermore, it is incumbent upon the Office to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up these assertions with acceptable and specific evidence. Id.

Since the specification is presumptively enabled, the burden fall on the Office to rebut this presumption. In particular, in support of any enablement rejection, the Office must submit evidence and facts, not merely conclusions and opinions. (See, e.g., Ex parte Reese, 40 USPQ2d 1221 (BPAI 1996)). The Office has failed to rebut the presumption.

Applicants submit that the specification fully enables how to practice the claimed invention. As attested to by Dr. Weiner, in the attached 37 CFR §1.132 Declaration, it is well known to those of skill in the art that antigenicity as determined by the binding of antibodies to

antigens reflects the immunogenicity of a polypeptide region. (Weiner Declaration, ¶ 5). As further attested by Dr. Weiner, methods for raising antibodies against an immunogenic composition comprising an immunogenic HCV polypeptide in substantially isolated form and measuring the binding of antibodies to the immunogenic composition are well known to those of skill in the art and are taught in the specification. (Weiner Declaration, ¶ 5). For example, the specification on page 59, line 23 through page 61, line 2, describes standard techniques known to those of skill in the art for raising antibodies against an immunogenic HCV composition and for measuring the binding of antibodies to the immunogenic composition. Generally these techniques involve: 1) injecting a selected mammal (e.g., mouse, rabbit, goat, etc.) with an HCVpolypeptide, 2) collecting the serum from the immunized animal, and 3) screening the serum for antibodies which bind to the immunogenic HCV polypeptide using routine techniques known in the field, including for example, a radioimmunoassay, as described in section IV.D. "Radioimmunoassay for Detecting HCV Antibodies in Serum" on page 178, line 1 through page 179, line 24, or an ELISA, as described in the specification on page 25, lines 5-9. (Weiner Declaration, ¶ 6). Thus, as attested by Dr. Weiner, as an expert in the field of hepatitis research, it is her opinion that the above referenced application provides sufficient information to a scientist of skill in the field applying routine procedures known in the field and materials available to that field to identify immunogenic HCV sequences. (Weiner Declaration, ¶ 7).

Moreover, the specification is replete with working examples of immunogenic HCV polypeptides (see for e.g. section IV.B.8.a. "Polypeptides Expressed in E. coli", page 147, line 7 through page 153, line 4). Applicants particularly point to the proven list of immunogenic polypeptides found on page 152 of the specification. Included on the list are representative immunogenic polypeptides from each of the claimed domains, including for example, clone CA279a which includes amino acids from the core domain of HCV (amino acids 1-120), clone CA290a which includes amino acids from the core and envelope domains of HCV (amino acids 120-400), clone CA74a which includes amino acids from the NS1 domain of HCV (amino acids 400-660), and clone 13i which includes amino acids from the NS1 and NS2 domains of HCV (amino acids 660-1050).

Applicants, therefore submit, that the specification provides ample guidance on how to practice the claimed invention. It is undisputed that the level of skill in the relevant art is very high. In addition, the specification, as well as the Examples, contain teachings of how to prepare and use the claimed immunogenic compositions.

The Office alleges that, "In order to identify a[n immunogenic] sequence, one must have a method of predicting which sequences would . . . contain an epitope . . . . Such methods are unknown in the art." First, Applicants submit that it is not necessary to know which sequences contain an epitope in order to determine whether or not a composition is immunogenic. As attested by Dr. Weiner, prospective polypeptide sequences need only be prepared and injected into a mammal with the appropriate carriers and/or adjuvants, as described in Section II.C. Preparation of Antigenic Polypeptides and Conjugation with Carrier - page 47, line 24 through page 53, line 36; and Section II.G. Preparation of Antibodies Against HCV Epitopes - page 59, line 23 through page 61, line 2, and then the serum collected and screened for antibodies which bind to the prospective polypeptide sequence using routine methods. Examples of routine screening methods include radioimmunoassay and ELISA, which are described in the specification on page 178, line 1 through page 179, line 24 and page 25, lines 5-9, respectfully. (Weiner Declaration, ¶ 8).

Moreover, according to Dr. Weiner, although it is not necessary to map a HCV epitope in order to practice the claimed invention such techniques are known to those of skill in the art and are taught in the specification. (Weiner Declaration, ¶ 9). For example, the specification teaches methods for screening for immunological activity using routine techniques known to those of skill in the art, including for example, radioimmunoassay and ELISA. By starting with, for example, 20-mer polypeptides, it would be routine to test each polypeptide for the presence of epitopes showing a desired reactivity using, for example, a radioimmunoassay or an ELISA, and then testing progressively smaller and overlapping fragments from an identified 20-mer to map the epitope of interest (page 50, lines 2-20). Screening such peptides for immunological activity employs routine procedures known to those of skill in the art. (Weiner Declaration, ¶ 9).

In addition, as attested by Dr. Weiner, it is also known to those of skill in the art to carry out computer analysis of protein sequences to identify potential epitopes, and then prepare

oligopeptides comprising the identified regions for screening. See for e.g. Hopp et al., *PNAS* (1981) 78:3824-3828. Such a computer analysis of the HCV amino acid sequence is shown in Figure 67, where the hydrophilic/hydrophobic character is displayed above the antigenic index (page 50, lines 20-32). (Weiner Declaration, ¶ 11).

The Office also expresses concern that the specification does not teach how to identify peptides which would have a reasonable expectation of not being cross-reactive with other flaviviruses. The claims, however, do not specify that the immunogenic polypeptide must be specific only for HCV, and therefore, the Office's objection is without legal basis. Further, as described in the specification, in some cases it would be an advantage for the peptide to react with both anti-HCV, and other anti-flavivirus antibodies. ("It is possible that shared epitopes between flaviviruses and HCV will give rise to protective antibodies against one or more of the disorders caused by these pathogenic agents. Thus, it may be possible to design multipurpose vaccines based upon this knowledge." Page 56, lines 26-34). Therefore, there is no need as determined by the claimed invention to identify amino acid sequences which are specific only for HCV and not for other flaviviruses. Nevertheless, as attested by Dr. Weiner, the specification does in fact teach how to identify polypeptides which bind anti-HCV antibodies and not to antibodies directed against other viruses. As described in the specification, on page 185, line 20 through page 186, line 5, the polypeptides of interest are first tested for immunoreactivity against sera from individuals which have been infected with non-HCV viruses (e.g. flaviviruses, HAV, HBV, etc...) using standard techniques, including for example solid phase RIA. By comparison, then, those polypeptides which bind specifically to antibodies in sera from those infected with HCV can be determined. (Weiner Declaration, ¶ 12).

The only evidence provided by the Office in support of its allegations is the reference Hopp et al. 1981 PNAS 78:3824-3829 (referred to hereinafter as "Hopp"). Hopp, in fact, supports Applicants' claims. As quoted by the Office, Hopp et al. "discloses computer algorithms for identifying regions of amino acid sequences likely to be antigenic, or immunoreactive, with an antibody based upon regions of hydrophobicity." On page 50-53 of Applicants' specification, methods for identifying HCV amino acid sequences comprising epitopes, including for example, computer analysis methods are provided.

It is also known to carry out a computer analysis of a protein sequence **to identify potential epitopes**, and then prepare oligopeptides comprising the identified regions for screening. Such a computer analysis of the HCV amino acid sequence is shown in Figure 67, where the hydophilic/hydrophobic character is displayed above the antigen index.

Specification, page 50, lines 20-28.

The Office expresses concerns that the computer methods described in Hopp do not speak to the immunospecificity of antibodies that bind specific regions of HCV amino acid sequences. First, none of the pending claims require the compositions of the invention to elicit an immune response which is immunospecific to HCV. As determined by the claims, the elements that are required to practice the claimed invention are: 1) an immunogenic HCV polypeptide; 2) in substantially isolated form; and 3) wherein said immunogenic polypeptide comprises a region selected from the group consisting of an envelope domain, a core domain, a NS1 domain and a NS2 domain of an HCV genome and immunogenic fragments and combinations thereof. Second, the specification specifically teaches that in some cases it would be an advantage for the peptide to react with both anti-HCV and other anti-flavivirus antibodies ("It is possible that shared epitopes between flaviviruses and HCV will give rise to protective antibodies against one or more of the disorders caused by these pathogenic agents. Thus, it may be possible to design multipurpose vaccines based upon this knowledge." Page 56, lines 26-34). Furthermore, Applicants submit that the specification thoroughly describes how to make and use compositions which produce immune responses which are specific to HCV. See, for example, Section IV.B.8. Expression and Antigenicity of Polypeptides Encoded in HCV cDNA, which describes the expression of HCV polypeptides encoded in a number of HCV cDNAs as well as tests performed on the expression products for antigenicity by direct immunological screening of the colonies using a modification of the method described in Helfman et al. (1983). See the table on page 152 for examples of clones encoding polypeptides of proven reactivity with sera from NANBH patients.

The Office also expresses concern that "even using the methods of Hopp, there is no way for predicting which amino acids in a sequence are critical for antigenicity of an epitope" and "that there is no direction in the specification indicating which elements of a particular sequence

would fold properly to present HCV epitopes". Applicants submit that the claims do not necessitate knowing the exact portions of a protein which are necessary to produce an immune response. Instead the claims are directed to an immunogenic composition comprising an immunogenic HCV polypeptide in substantially isolated form wherein the immunogenic polypeptide comprises a region selected from the group consisting of an envelope domain, a core domain, a NS1 domain and a NS2 domain of an HCV genome and immunogenic fragments and combinations thereof. As disclosed in the specification and pointed out by the Office an immunogenic polypeptide is a polypeptide that elicits cellular and/or humoral response. The Office further points out that immunological responses include antibodies that bind epitopes of immunogenic compositions. Applicants submit that techniques for raising antibodies against an immunogenic composition and screening for antibodies that bind to immunogenic composition are standard and well known to those of skill in the art, including for example, injecting a mammal with a HCV polypeptide, collecting the serum from the immunized animal, and screening the serum for antibodies which bind the immunogenic polypeptide using a radioimmunoassay or an ELISA. (Weiner Declaration, ¶ 6). Such teachings are fully described throughout the specification. See for e.g., sections II.G. "Preparation of Antibodies Against HCV Epitopes", lines 23-36 which describes using immunogenic HCV polypeptides to produce antibodies by immunizing a selected mammal with an immunogenic polypeptide bearing an HCV epitope; section IV.D. "Radioimmunoassay for detecting HCV antibodies in Serum" on page 178, line 1 through page 179, line 24, which describes solid phase radioimmunoassays for detecting antibodies to HCV antigens.

Hopp, does not, therefore, provide the Office with the requisite evidence for showing that there is a reasonable basis to question the presumptively sufficient disclosure made by Applicants.

The Office has not pointed to any evidence in the record supporting its position that the specification as filed is not enabling for the present claims, such that one of ordinary skill in the field of the invention, given the information and sequence of HCV from Applicants' specification could not (1) identify a polypeptide antigen that would be recognized by anti-HCV antibodies or

(2) raise anti-HCV antibodies. Presumably, therefore, the basis for the rejection is within the personal knowledge of the Examiner.

Under MPEP § 706.02 (a) and 37 CFR § 1.107(b) "[w]hen a rejection in an application is based on facts within the personal knowledge of an employee of the Office ... the reference must be supported, when called for by the Applicant, by the affidavit of such employee..." 37 CFR § 1.107(b), emphasis added. In the response filed April 29, 1997 response, p. 18, lines 9-10, Applicants specifically requested that the Office support its contentions with facts in the record or comply with 37 CFR § 1.107(b). The Office has not yet supported its contention. The Office has dismissed the evidence of the record, and maintained unsupported assertions that the present claims are not enabled with respect to immunogenic peptides. Also, see *In re Alton* 76 F.3d 1168, 1176 (Fed. Cir. 1996), wherein the Federal Circuit held that an examiner can not rebut a declaration with conclusory statements in order to maintain a § 112, paragraph 1 rejection. Thus, maintaining this rejection in the absence of the requested evidence violates well settled case law.

Applicants submit that the enablement of the claims is supported by extensive evidence found in the original specification, as well as the attached 37 C.F.R. §1.132 Declaration of record by Dr. Weiner.

For all of the above stated reasons, Applicants contend that the claims meet the requirements for enablement under 35 U.S.C. § 112 ¶ 1 and request that the Examiner withdraw the objections to the specifications and the rejections under this paragraph.

If the Examiner wishes to maintain the rejections to the claims Applicants respectfully request that the Examiner submit an affidavit under 37 C.F.R. § 1.107(b) identifying those techniques which are necessary to practice the claimed invention that are not described in the present specification and not already known to the skilled practitioner of the art. In the absence of such evidence, withdrawal of this rejection is in order and is respectfully requested.

35 U.S.C. § 112, Second Paragraph Rejections:

Claim 47 was rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for referring to polypeptides encoded by either strand of the lambda-gt11 cDNA

libraries deposited with the ATCC. Specifically the use of the noncoding strand of HCV to encode polypeptides is questioned. Applicants submit that the "either strand" language refers to the lambda-gt11 cDNA libraries not necessarily the HCV sequences in isolation. This language covers polypeptides encoded within the HCV cDNA sequences in the libraries regardless of their orientation vis-à-vis the lambda-gt11 vector. Nevertheless, in an attempt to expedite prosecution, claim 47 has been canceled and has been replaced by claim 104. This new claim does not contain the phrase "either strand." Thus the Office's concerns regarding the use of the term "either strand" in the claims has been addressed.

Applicants have amended the pending claim set to eliminate the only § 112, second paragraph issue identified in the outstanding Office Action. Applicants therefore request that the Office withdraw the rejections under 35 U.S.C. § 112, second paragraph.

35 U.S.C. § 102 Rejections:

Claims 40-51 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Bradley, J. Virol. Meth. (1985) 10: 307-309 (referred to hereinafter as "Bradley"); He et al., J. Infect. Dis. (1987) 136(4):636-640 (referred to hereinafter as "He"); and Prince et al. J. Med. Virol. (1985) 16:119-125 (referred to hereinafter as "Prince"). While claims 40-51 have been cancelled, the subject matter of claims 40 to 51 have been addressed in new claims 88 to 114. Applicants respectfully traverse the rejection and supporting remarks.

Rejection for anticipation or lack of novelty under 35 U.S.C. § 102 (b) requires that each and every limitation of the claimed invention be disclosed in a single prior art reference. In re Spada, 911 F.2d 705, 708 (Fed. Cir. 1990). In addition, the prior art reference must contain an enabling disclosure such that one skilled in the art could take the description, combine it with his own knowledge of the particular art, and thereby be put in possession of the claimed invention. See In re Sasse, 629 F.2d 675, 681 (CCPA 1980).

For the below stated reasons, Applicants submit that neither Bradley, He nor Prince disclose each.and every limitation of the pending claims. Applicants further submit that none of the references is enabling for the Applicants' claimed subject matter.

In the present case, the immunogenic compositions of the pending claims are required to have the following elements: 1) be an immunogenic HCV polypeptide; 2) be in substantially isolated form; and 3) wherein the immunogenic polypeptide comprises a region selected from the group consisting of an envelope domain, a core domain, a NS1 domain and a NS2 domain of an HCV genome and immunogenic fragments and combinations thereof. None of the references cited by the Office describes how to make and use an immunogenic composition with all of these elements.

Bradley et al.

The Office alleges that Bradley discloses "several purified or isolated NANBV agents, which are infectious, and produce NANBH in chimpanzees". Even if the Office were correct (and as discussed below it is not) Applicants' claims disclose an immunogenic composition comprising an immunogenic hepatitis C virus (HCV) polypeptide. According to Dr. Weiner, other agents, including HEV, HDV and possibly HGV cause NANB hepatitis. The disclosure of a NANBV agent is not necessarily a HCV agent. (Weiner Declaration, ¶ 13). Furthermore, the authors of Bradley admit on page 314 that at the time, "[m]ore than 14 different virus-like structures have been described for NANB hepatitis, yet none has been irrefutably linked to the transmission of disease."

Nor does Bradley disclose an immunogenic HCV polypeptide in substantially isolated form. While Bradley does discuss at least two preparations that have undergone some purification and that may or may not contain some sort of viruses, they are only crude, whole viral preparations at best, and not polypeptides in substantially isolated form as specified in the claims. On page 315, Bradley describes the alleged isolation of a non-A non-B hepatitis tubule forming agent having a buoyant density in 1.24 g/cc of CsCl. However, as attested by Dr. Weiner, and supported in Hijikata et al., (1993) J. of Virology, 67:1953-1958 (copy attached), it is well known to those of skill in the art that HCV has a buoyant density of ~1.09 g/cc of CsCl. (Weiner Declaration, ¶ 16). Bradley, therefore, provides no evidence that he has isolated HCV, let alone an immunogenic HCV polypeptide in substantially isolated form. Moreover, the evidence of record provided by Applicants suggest that the alleged NANB agent disclosed by Bradley is not HCV.

The immunogenic compositions of the claimed invention further require that the immunogenic polypeptide comprises a region selected from the group consisting of an envelope domain, a core domain, a NS1 domain and a NS2 domain of an HCV genome and immunogenic fragments and combinations thereof. As attested by Dr. Weiner, however, it would not have been possible for one of skill in the art, without knowing the sequence of HCV or portions thereof, the genomic structure of HCV, the identity of HCV, or antibodies that identified HCV proteins to take the description in Bradley and combine it with his/her own knowledge of the art, and thereby be put in possession of an immunogenic hepatitis C virus (HCV) polypeptide in substantially isolated form, wherein said immunogenic polypeptide comprises a region selected from the group consisting of an envelope domain, a core domain, a NS1 domain and a NS2 domain of an HCV genome and immunogenic fragments and combinations thereof. (Weiner Declaration, ¶ 17).

Furthermore, the instant claims are directed to immunogenic HCV polypeptides. At no time does Bradley describe any sample as immunogenic or exhibiting any characteristic consistent with immunogenicity. When he does discuss the immunogenicity of a NANB virus it is only a theoretical discussion and only with respect to an infection by a whole living virus. Even under these circumstances, however, he proposes that "apparent protection of a previously NANB-infected chimpanzee from infection with a second challenge inoculum (and a distinct agent) could simply be due to viral interference rather than the presence of homologous, neutralizing antibody." (See Bradley page 309). So, the only instance of protection from infection that Bradley even contemplates in his article 1) is not observed in association with any of his samples, 2) is completely theoretical and not empirically demonstrated anywhere, 3) is only attributed to infection by a whole living virus and not a polypeptide in substantially isolated form, 4) is never associated with a confirmed case of HCV, and 5) is attributable to viral interference due to infection and not any form of immune response.

The Bradley reference simply fails to demonstrate, or even claim, any evidence of an immunogenic composition which approximates the claimed invention and therefore does not qualify as an anticipatory reference under § 102 (b).

In addition to disclosing each and every element of the claimed invention, an anticipatory reference must contain an enabling disclosure such that one skilled in the art could take the description, combine it with his own knowledge of the particular art, and thereby be put in possession of the claimed invention. See In re Sasse, 629 F.2d 675, 681 (CCPA 1980). For the reasons discussed below, Bradley does not provide an enabling disclosure.

The Office alleges that Bradley discloses various viral preparations all of which comprise at least 8 amino acids of HCV sequence, and provoke an immune response. Yet, according to Dr. Weiner it would not have been possible for one of skill in the art, without knowing the sequence of HCV or portions thereof, the genomic structure of HCV, the identity of HCV, or antibodies that identified HCV protein, to take the description in Bradley and combine it with his/her own knowledge of the art, and thereby be put in possession of the claimed invention. (Weiner Declaration, ¶ 17). Specifically, the claims are directed not only to HCV polypeptides in substantially isolated form but further specify domains of HCV (i.e. core, envelope, NS1 and NS2) which could not be and were not identified until Applicants own work. (Weiner Declaration, ¶ 16). As attested by Dr. Weiner, the sequence of HCV or portions thereof, the genomic structure of HCV, the identity of HCV, or antibodies that identified HCV protein were not available to those of skill in the art until after 1989. (Weiner Declaration, ¶ 18) Therefore, because Bradley neither discloses the sequence of HCV or portions thereof, the genomic structure of HCV, the identity of HCV, or antibodies that identified HCV protein and such information was not known to those of skill in the art until after 1989, Bradley cannot be deemed an enabling disclosure for the present claims.

Furthermore, it is unclear why the Office makes reference to the "F" and "H" strains isolated by Feinstone. Bradley does not use nor propose to use either of these strains in his studies.

For all of the above stated reasons, Applicants submit that Bradley does not meet the legal requirements for an anticipatory reference under 35 U.S.C. § 102 (b). Thus Applicants respectfully request that the 35 U.S.C. § 102 (b) be reconsidered and withdrawn.

He et al.

Like Bradley, He discloses the isolation of an alleged NANB hepatitis virus. The Applicants' claims, however, disclose an immunogenic hepatitis C virus polypeptide. As attested by Dr. Weiner, the disclosure of a NANBV is not necessarily a HCV agent. (Weiner Declaration, ¶ 13).

Also like Bradley, He only discloses the preparation of a whole, live virus preparation. They do not disclose an immunogenic HCV polypeptide in substantially isolated form. According to Dr. Weiner, He does not describe the isolation of the polypeptide from the virus' lipid envelope or any other cellular components with which the viral polypeptide is naturally associated in the viral particle. (Weiner Declaration, ¶20). Only crude serum filtrate maintaining infectivity is produced; i.e., no isolated peptides are disclosed. *Id.* Such a crude inoculum could have contained any number of viruses, including multiple forms of NANB hepatitis. *Id.* Moreover, even the source of the Hutchinson inoculum suggests that "the H inoculum contains two [agents]." (Feinstone et al., Viral Hepatitis: 1981 International Symposium. Philadelphia: Franklin Institute Press, 1982:295-304, at 295). Therefore, as attested by Dr. Weiner, He fails to disclose a viral polypeptide in "substantially isolated form". (Weiner Declaration, ¶ 19).

In addition, He discloses no evidence of an immune response of any kind in the chimpanzees that were injected with their whole viral preparations. He measures the activity levels of certain enzymes, including alanine aminotransferase, aspartate aminotransferase, isocitric dehydrogenase, and gamma-glutamyl transferase, all of which are associated with liver damage. They also perform electron microscopic analyses of liver biopsies, but they do not disclose any information relating to immunogenicity.

Therefore, the He reference fails to disclose a polypeptide in substantially isolated form, fails to disclose or even claim any evidence of an immune response, and fails to positively identify the virus shown as HCV. As discussed above, in order to anticipate the claimed invention, the He reference would have to demonstrate at least all three of these elements.

Nor does He provide an enabling disclosure for the claimed invention, namely, an immunogenic HCV polypeptide, in substantially isolated form, wherein said immunogenic polypeptide comprises a region selected from the group consisting of an envelope domain, a core

domain, a NS1 domain and a NS2 domain of an HCV genome and immunogenic fragments and combinations thereof. In He, the authors used membrane filtration to estimate the size of one strain of NANB hepatitis virus. He et al. reported that strain H is 30-60 nm in diameter.

As attested to by Dr. Weiner, one of skill in the art at the time would not have been able to take the information disclosed in He et al. i.e., that strain H has an estimated size between 30 and 60 nm in diameter, and combine it with his/her own knowledge of the art at the time, and thereby be put in possession of the claimed invention. (Weiner Declaration, ¶ 21). According to Dr. Weiner, in order to practice the claimed invention, which is directed not only to HCV but to specific domains of HCV (i.e. core, env, NS-1, NS-2), one would need to know the sequence of HCV or portions thereof, the genomic structure of HCV, the identity of HCV, or antibodies that identified HCV proteins. *Id.* The sequence of HCV or portions thereof, the genomic structure of HCV, the identity of HCV, or antibodies that identified HCV proteins were not known to those of skill in the art until after 1989. *Id.*

In addition, according to Dr. Weiner, there are a number of viruses that have the same characteristics as those disclosed in He. (Weiner Declaration, ¶ 22). The authors themselves express their uncertainty with regard to the identity of the alleged NANB hepatitis virus:

> Only four recognized groups of viruses are small (30-60 nm in diameter) and contain essential lipids: the alphaviruses, the flaviviruses, the hepadnaviruses, and the hepatitis D virus . . . . . At present it is not possible to determine whether NANB hepatitis virus is related to one of these four groups of viruses or whether it is a member of a new group . . . . Additional characterization of HDV, including filtration, is in progress.
>
> He at page 639-640.

Furthermore, it is interesting to note that one of the co-authors on the He reference, Harvey J. Alter, in a 1991 publication, attested to the fact that Applicants were the first to discover HCV and identify it as an etiologic agent of blood-bourne NANB hepatitis. Dr. Alter stated:

> "In an unprecedented approach to viral discovery the hepatitis C virus (HCV) was cloned before it was established by conventional methods of viral detection or by genomic characterization....Although considerable knowledge of the non-A, non-B hepatitis virus was accrued through clinical observation and studies of

> transmission in chimpanzees, the agent eluded serologic detection for more than a decade. Identification was finally achieved through a unique application of molecular biologic techniques." H.J. Alter, Annals of Internal Medicine (1991) 115: 644-649 at 644 [cites omitted, emphasis added].

Thus, even a co-author on the He reference admits that HCV and its causal relationship with NANB hepatitis was unidentified prior to Applicants' discovery and characterization of this virus.

For all the above-stated reasons, Applicants submit that He does not meet the legal requirements for an anticipatory reference under 35 U.S.C. § 102 (b). Thus, Applicants respectfully request that the 35 U.S.C. § 102 (b) be withdrawn.

Prince et al.

The Office alleges that Prince discloses a method of inactivating the Hutchinson strain by treatment with beta-propiolactone. However, like Bradley and He, Prince neither discloses a composition with each of the claimed elements nor does it describe how to make and use an immunogenic composition with all of the claimed elements.

Like Bradley and He, Prince describes an alleged NANB hepatitis virus. The Applicants' claims, however, are directed to an immunogenic hepatitis C virus polypeptide. As attested by Dr. Weiner, other agents, including HEV, HCV and possibly HGV cause NANB hepatitis. (Weiner Declaration 13).

Second, the Prince team demonstrates no evidence of an immune response of any kind. Quite the contrary, Prince showed that their treated inoculum did not protect the chimpanzees from infection by subsequent injection with untreated inoculum.

Third, Prince fails to disclose any kind of method for isolating a viral polypeptide in substantially isolated form, let alone a HCV polypeptide wherein the HCV polypeptide comprises a region selected from the group consisting of an envelope domain, a core domain, a NS1 domain, a NS2 domain of an HCV genome and fragments and combinations thereof.

Therefore, the Prince reference fails to disclose any purification process whatsoever, fails to disclose or even claim any evidence of an immune response, and fails to positively identify

their viral infection as HCV. As discussed above, in order to anticipate the present invention, the Prince reference would have to demonstrate all three of these elements.

Furthermore, Prince fails to provide an enabling disclosure. As attested by Dr. Weiner, it would not have been possible for one of skill in the art, without knowing the sequence of HCV or portions thereof, the genomic structure of HCV, the identity of HCV, or antibodies that identified HCV proteins, to take the description in Prince and combine it with his/her own knowledge of the art, and thereby be put in possession of the claimed invention. (Weiner Declaration, ¶ 25). Specifically, the claims are directed not only to HCV polypeptides in substantially isolated form but further specify domains of HCV (i.e. core, envelope, NS1 and NS2) which could not be and were not identified until Applicants own work. Therefore, because Prince neither discloses the sequence of HCV or portions thereof, the genomic structure of HCV, the identity of HCV, or antibodies that identified HCV proteins, and such information was not known to those of skill in the art until after 1989, Prince cannot be deemed an enabling disclosure and therefore does not meet the legal requirements for an anticipatory reference under § 102 (b).

In view of the evidence discussed above, neither Bradley, He nor Prince report or enable the claimed immunogenic compositions, nor provide any definitive evidence that HCV was the virus with which they were working. As such, these references do not teach all of the limitations of the claims and would not enable the subject matter of Applicants' previously pending or currently pending claims. Applicants therefore request that the rejections under 35 U.S.C. § 102 (b) be reconsidered and withdrawn.

The evidence on the record, including a Declaration by Dr. Weiner under 37 C.F.R. § 1.132, shows that neither neither Bradley, He nor Prince anticipate Applicants' claims. In the event that these references are not withdrawn as anticipatory references under 35 U.S.C. § 102 (b), Applicants request that the Examiner provide supporting evidence, either in the form of publications or an Examiner's affidavit under 37 C.F.R. 107(b), to refute Applicants' contentions concerning the non-enablement of these references for immunogenic HCV polypeptides.

Summary

The submitted claims comply with the requirements of 35 U.S.C. § 112, ¶ 1 and ¶ 2, and with 35 U.S.C. § 102. Accordingly, Applicants request an early notification of allowability of the claims. In the event that the Examiner wishes to further discuss the above-referenced application, she is invited to telephone Applicant's attorney at the telephone number listed below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 223002006313. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: November 17, 1998 By: Gladys H. Monroy

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Enclosures:

-Copy of an unsigned (signed duplicate copy will be mailed shortly) Declaration by Amy Weiner, Ph.D under 37 C.F.R. § 1.132 (9 pages)
-Reference by Hijikata et al., J. Virol. 67:1953-1958 (1993) (7 pages)